Articular Cartilage of the Human Knee Joint: In Vivo Multicomponent T2 Analysis at 3.0 T[1]

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Purpose: To compare multicomponent T2 parameters of the articular cartilage of the knee joint measured by using multicomponent driven equilibrium single-shot observation of T1 and T2 (mcDESPOT) in asymptomatic volunteers and patients with osteoarthritis.

Materials and Methods: This prospective study was performed with institutional review board approval and with written informed consent from all subjects. The mcDESPOT sequence was performed in the knee joint of 13 asymptomatic volunteers and 14 patients with osteoarthritis of the knee. Single-component T2 ($T2_{Single}$), T2 of the fast-relaxing water component ($T2_F$) and of the slow-relaxing water component ($T2_S$), and the fraction of the fast-relaxing water component (F_F) of cartilage were measured. Wilcoxon rank-sum tests and multivariate linear regression models were used to compare mcDESPOT parameters between volunteers and patients with osteoarthritis. Receiver operating characteristic analysis was used to assess diagnostic performance with mcDESPOT parameters for distinguishing morphologically normal cartilage from morphologically degenerative cartilage identified at magnetic resonance imaging in eight cartilage subsections of the knee joint.

Results: Higher cartilage $T2_{Single}$ ($P < .001$), lower cartilage F_F ($P < .001$), and similar cartilage $T2_F$ ($P = .079$) and $T2_S$ ($P = .124$) values were seen in patients with osteoarthritis compared with those in asymptomatic volunteers. Differences in $T2_{Single}$ and F_F remained significant ($P < .05$) after consideration of age differences between groups of subjects. Diagnostic performance was higher with F_F than with $T2_{Single}$ for distinguishing between normal and degenerative cartilage ($P < .05$), with greater areas under the curve at receiver operating characteristic analysis.

Conclusion: Patients with osteoarthritis of the knee had significantly higher cartilage $T2_{Single}$ and significantly lower cartilage F_F than did asymptomatic volunteers, and receiver operating characteristic analysis results suggested that F_F may allow greater diagnostic performance than that with $T2_{Single}$ for distinguishing between normal and degenerative cartilage.

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Osteoarthritis is a highly prevalent and severely debilitating chronic disease (1,2). Characteristic changes in the cartilage macromolecular matrix occur with osteoarthritis, including a decrease in proteoglycan content and disruption of the highly organized collagen fiber network (3–5). Various quantitative magnetic resonance (MR) imaging techniques have been used to identify changes in the composition and ultrastructure of articular cartilage in patients with osteoarthritis (6). The T2 of cartilage is one of the most commonly used MR imaging parameters and has been shown to be sensitive for detection of cartilage degeneration in ex vivo specimens (7) and human subjects (8–12). However, cartilage T2 is a complex measurement that is influenced by multiple factors including water and macromolecular content (13–16), organization of the collagen fiber network (17–19), cartilage loading (20–22), and orientation of cartilage relative to the main magnetic field (23). Thus, changes in cartilage T2 may be difficult to interpret and sometimes challenging to detect because of the multiple potentially competing biologic factors that influence the measurement.

Quantitative MR imaging techniques that allow measurement of multicomponent T2 values have been used to improve the specificity of T2 analysis of cartilage (24–28). Nuclear MR spectroscopic studies have allowed identification of three exchangeable water components in cartilage: extremely fast-relaxing water tightly bound to collagen, fast-relaxing water tightly bound to proteoglycan, and slow-relaxing bulk water loosely bound to the hydrophilic glycosaminoglycan side chains of proteoglycan with T2 values of 2.2, 25.2, and 96.3 msec, respectively (24). Because of the low fraction and difficulty in measuring the water tightly bound to the collagen component, which has an extremely short T2 (24), most multicomponent T2 mapping techniques involve the use of bicomponent models that allow assessment of only the fast-relaxing water tightly bound to proteoglycan and slow-relaxing bulk water loosely bound to the hydrophilic glycosaminoglycan side chains of proteoglycan components of cartilage (25–28). Authors of previous studies have shown that the fraction of the fast-relaxing water tightly bound to the proteoglycan component is a sensitive and specific measure of the proteoglycan content of cartilage (24–26). However, authors of previous multicomponent T2 mapping studies (24–28) have been limited by their use of Carr-Purcell-Meiboom-Gill techniques with long acquisition times, which allowed for cartilage assessment on only a single section of ex vivo specimens.

Multicomponent driven equilibrium single-shot observation of T1 and T2 (mcDESPOT) is a rapid method for multicomponent T2 mapping (29–34). The use of mcDESPOT allows acquisition of three-dimensional (3D) voxel-based measurements of the fractions and T2 values of the fast-relaxing and slow-relaxing water components of the articular cartilage of the human knee joint at 3.0 T with high spatial resolution, large volume coverage, and relatively short imaging time, which makes it feasible for use in clinical practice and osteoarthritis research studies (35). Authors of few previous studies have investigated multicomponent T2 parameters in human articular cartilage. Therefore, it remains unknown how cartilage degeneration in human subjects leads to changes in the fractions and T2 values of the different water components of cartilage. Thus, this study was performed to compare multicomponent T2 parameters of the articular cartilage of the knee joint measured by using mcDESPOT in asymptomatic volunteers and patients with osteoarthritis.

Advances in Knowledge

- Single-component T2 and the fraction of the fast-relaxing water component were significantly different ($P < .05$) between asymptomatic volunteers and patients with osteoarthritis of the knee.
- Use of the fraction of the fast-relaxing water component value showed significantly higher ($P < .05$) diagnostic performance than did use of single-component T2 for distinguishing morphologically normal cartilage from morphologically degenerative cartilage in the knee joint.

Implication for Patient Care

- The fraction of the fast-relaxing water component measured at 3.0 T by using multicomponent-driven equilibrium single-shot observation of T1 and T2 may allow greater diagnostic performance than does single-component T2 for detection of cartilage degeneration in the human knee joint.

Materials and Methods

Study Group

Our prospective study was performed between June 1, 2013, and February 1, 2014, in compliance with Health

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Abbreviations:
AUC = area under the curve
BLOKS = Boston-Leeds osteoarthritis knee scoring
CI = confidence interval
F_F = fraction of the fast-relaxing water component
FSE = fast spin echo
mcDESPOT = multicomponent driven equilibrium single-shot observation of T1 and T2
$T2_F$ = T2 of the fast-relaxing water component
$T2_{Single}$ = single-component T2
$T2_S$ = T2 of the slow-relaxing water component
3D = three-dimensional

Author contributions:
Guarantors of integrity of entire study, F.L., J.J.W., R.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, F.L., A.S., R.G.S., R.K.; clinical studies, F.L., R.K.; experimental studies, F.L., A.S., J.J.W., W.F.B., R.K.; statistical analysis, F.L., K.W.C., W.F.B.; and manuscript editing, all authors

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Conflicts of interest are listed at the end of this article.

Insurance Portability and Accountability Act regulations and with approval from our institutional review board. All subjects signed written informed consent forms before their participation in the study. The study group consisted of 13 asymptomatic volunteers (10 men; average age, 26.6 years; range, 25–32 years; three women; average age, 32.0 years; range, 20–38 years) and 14 patients with osteoarthritis of the knee (nine men; average age, 51.5 years; range, 42–58 years; five women; average age, 54.5 years; range, 45–62 years). The sample size was selected by using a power analysis based on data obtained from a previously performed study (8) of cartilage T2 in which the authors compared volunteers and patients with osteoarthritis of the knee. The power analysis was performed by using two-sample Student *t* tests with 80% power and a significance level of .05 and was designed to allow detection of significant differences in cartilage T2 between volunteers and patients with osteoarthritis in at least three cartilage subsections in the knee joint.

All volunteers were selected from a database of individuals at our institution who had expressed interest in participating in MR imaging research and who had no history of knee pain, trauma, or surgery. All patients were recruited from the clinic of a fellowship-trained sports medicine specialist (J.J.W., with 8 years of clinical experience). All patients received a diagnosis of osteoarthritis during their routine clinical work-up according to standardized criteria that included chronic knee pain and stiffness for a minimum of 6 months and the presence of definitive grade 2 osteophytes on standing anterior-posterior knee radiographs (36,37). Exclusion criteria included a history of knee surgery, inflammatory arthritis, crystalline-induced arthritis, septic arthritis, and contraindication to MR imaging. Fourteen of 24 consecutive patients who received a diagnosis of osteoarthritis of the knee during their routine clinical work-up and who met the inclusion criteria were recruited, and 10 patients chose not to participate. Eight patients had Kellgren-Lawrence grade 2 osteoarthritis, while six patients had Kellgren-Lawrence grade 3 osteoarthritis (38).

MR Imaging Examination

All subjects underwent MR imaging examination of the knee joint with the same 3.0-T imager (Discovery MR750; GE Healthcare, Waukesha, Wis) and an eight-channel phased-array extremity coil (InVivo, Orlando, Fla). Foam padding was used to secure the knee firmly in the coil to minimize subject motion during the MR imaging examination. To assess the repeatability of cartilage multicomponent T2 measurements, the MR examination was performed twice on both knee joints in five of the volunteers (five men; average age, 29.2 years; range, 28–32 years). The subjects exited the imager and were allowed to rest in a sitting position for 10 minutes between examinations.

All MR imaging examinations consisted of the mcDESPOT sequence and a frequency-selective fat-suppressed 3D fast spin-echo (FSE) sequence performed on the sagittal plane through the knee joint. The 3D FSE sequence was performed with the following parameters: repetition time msec/echo time msec, 2216/23.6; field of view, 16 cm; matrix, 384 × 384; section thickness, 1.0 mm; bandwidth, 31.2 kHz; number of sections, 96; signal average, one; and imaging time, 7 minutes. The mcDESPOT sequence was a custom-made MR imaging pulse sequence consisting of a series of conventional spoiled gradient-echo and balanced steady-state free-precession sequences that are commercially available on the MR imaging platforms of all vendors. Eight spoiled gradient-echo sequences were performed with the following parameters: 4.9/2.3; and flip angles, $\alpha = 3°, 4°, 5°, 6°, 7°, 9°, 13°$, and $18°$. Eight balanced steady-state free-precession sequences were performed with the following parameters: 5.6/2.8; and flip angles, $\alpha = 2°, 5°, 10°, 15°, 20°, 30°, 40°$, and $50°$. Two balanced steady-state free-precession sequences were performed at each flip angle with radiofrequency phase cycling ($\varphi = 0°$ and $180°$) to remove the effects of balanced steady-state free-precession banding artifacts and to provide an estimate of the B_0 field. An additional inversion recovery spoiled gradient-echo sequence was performed with the following parameters: 4.9/2.3; inversion time msec, 450; and flip angle, $\alpha = 5°$ to estimate the transmit B_1 field. All sequences were performed by using the following parameters: field of view, 16 cm; matrix, 256 × 256; section thickness, 3 mm; bandwidth, 83.3 kHz; number of sections, 32; number of signals acquired, one. Total imaging time for the mcDESPOT sequence was 17 minutes.

Cartilage T2 Single- and Multicomponent Map Reconstruction

Multicomponent T2 maps of articular cartilage were reconstructed from the mcDESPOT source images with in-house software developed by using a high-level technical computing language and interactive environment (MATLAB 2010b; MathWorks, Natick, Mass). Single-component T2 ($T2_{Single}$) maps were created by using the driven equilibrium single-shot observation of T2 full-modeling reconstruction method (33). Results of previous studies have shown high pixel-by-pixel correlation between cartilage $T2_{Single}$ measurements obtained by using mcDESPOT and those obtained by using conventional Carr-Purcell-Meiboom-Gill techniques (35). Multicomponent T2 maps for the fast-relaxing water component ($T2_F$) and the slow-relaxing water component ($T2_S$) and maps for the fraction of the fast-relaxing water component (F_F) were created by using the two-pool mcDESPOT reconstruction method (29–31). The mcDESPOT method fits the observed spoiled gradient-echo and balanced steady-state free-precession signal at various flip angles with the use of the mathematical model described in the Appendix E1 (Fig E1 [online]). Image registration software (Flexible Image Registration Toolbox; Functional Magnetic Resonance Imaging of the Brain Analysis Group, Oxford University, England) was

used during the reconstruction process to correct for any subject motion that may have occurred between the multiple sequences.

Image Analysis

Quantitative cartilage analysis was performed by a research assistant (F.L., with 4 years of experience in segmentation) under the supervision of a fellowship-trained musculoskeletal radiologist (R.K., with 12 years of clinical experience) by using in-house software developed in the computing language and interactive environment (MATLAB, Mathworks). To investigate depth-dependent variations in multicomponent T2 parameters, pixel-by-pixel measurements of $T2_{Single}$, $T2_F$, $T2_S$, and F_F were plotted along a linear region of interest extending from the cartilage-bone interface to the articular surface in a single section through patellar cartilage in a randomly chosen asymptomatic volunteer. The articular cartilage on all sagittal 3D FSE sections through the knee joint in all subjects was segmented semiautomatically. Eight cartilage subsections were defined on the 3D FSE images, including the patella, trochlea, central medial femoral condyle, posterior medial femoral condyle, central lateral femoral condyle, posterior lateral femoral condyle, medial tibial plateau, and lateral tibial plateau as shown in Figure 1. The anterior margins of the anterior horn of the menisci were used to separate the trochlea from the central femoral condyles, while the posterior margins of the posterior horn of the menisci were used to separate the central femoral condyles from the posterior femoral condyles.

Cartilage thickness was calculated by exploring the 3D pixel data of the contours placed around articular cartilage on the 3D FSE images. The *x* and *y* coordinates of points were extracted on the basis of the locations of these pixels in each image, while the z coordinates were extracted on the basis of the section thickness and section indexes. The points in each image were patched into 3D triangular meshes, and the meshes were expressed as lists of triangular faces and sets of three vertices that form the triangles. The cartilage thickness was measured by calculating the minimum Euclidian distance from each triangle on the inner and outer cartilage boundary. The mean thickness was calculated as the average value of all MR image sections for each cartilage subsection. The average $T2_{Single,}$ $T2_F$, $T2_S$, and F_F in each cartilage subsection was measured by superimposing the 3D FSE contours of each subsection over the cartilage $T2_{Single}$, $T2_F$, $T2_S$, and F_F maps. Cartilage $T2_{Single}$, $T2_F$, $T2_S$, F_F, and thickness of the entire knee joint were calculated by averaging the values measured in all eight cartilage subsections.

Morphologic joint analysis was performed by a fellowship-trained musculoskeletal radiologist (R.K., with 12 years of clinical experience) who was blinded to whether a subject was an asymptomatic volunteer or a patient with osteoarthritis. The radiologist used the sagittal 3D FSE images and axial and coronal reformatted 3D FSE images generated by using the volumetric source data to grade the severity of degeneration in each cartilage subsection in the knee joint by using Boston-Leeds Osteoarthritis Knee Scoring (BLOKS) system (39).

Figure 1

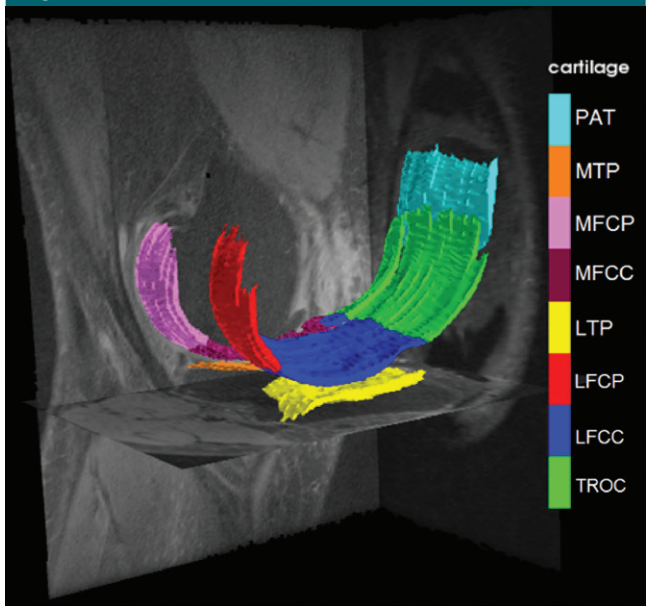


Figure 1: Schematic illustration shows 3D cartilage segmentation of knee joint in a 25-year-old asymptomatic male volunteer. Colored 3D contours created from 3D FSE images were used to delineate articular cartilage of patella (*PAT*), trochlea (*TROC*), central medial femoral condyle (*MFCC*), posterior medial femoral condyle (*MFCP*), central lateral femoral condyle (*LFCC*), posterior lateral femoral condyle (*LFCP*), medial tibial plateau (*MTP*), and lateral tibial plateau (*LTP*). Contours were superimposed over cartilage $T2_{Single}$, $T2_F$ $T2_S$, and F_F maps to measure average $T2_{Single}$, $T2_F$, $T2_S$, and F_F values in each cartilage subsection.

Statistical Analysis

Statistical analysis was performed by using MATLAB and the R programming environment (R programming environment, Version 2.3.1; R Foundation of Statistical Imaging; Vienna, Austria; http://www.*R*-project.org). For all tests, a statistically significant difference in MR imaging parameters between groups of subjects was defined as a *P* value less than .05. The Holm-Bonferroni correction method was used to adjust all *P* values to account for multiple comparisons (40).

Coefficients of variation were used to assess the repeatability of cartilage multicomponent T2 measurements on each cartilage subsection of the knee joint. Coefficients of variation were defined as the mean divided by the standard deviation of the multicomponent T2 measurements obtained by using the two repeat mcDESPOT sequences performed in the same knee of the same volunteers. Coefficients of variation for repeat cartilage multicomponent T2 measurements of the entire knee joint were also calculated by averaging the values measured in all eight cartilage subsections.

To minimize type I error due to comparison of multiple MR imaging parameters on multiple cartilage subsections, average cartilage $T2_{Single}$, $T2_F$, $T2_S$, F_F, and thickness of the entire knee joint were first compared between the groups of subjects. Wilcoxon rank-sum tests were used to compare average cartilage $T2_{Single}$, $T2_F$, $T2_S$, F_F, and thickness of the entire knee joint between volunteers and patients. Kruskal-Wallis one-way analysis of variance was used to compare average cartilage $T2_{Single}$, $T2_F$, $T2_S$, F_F, and thickness of the entire knee joint among volunteers, patients with Kellgren-Lawrence grade 2 osteoarthritis, and those with grade 3 osteoarthritis of the knee. Multivariate linear regression models were then used to account for age differences between groups of subjects in the analysis by using both MR imaging parameters and age as continuous variables to distinguish between groups of subjects. Wilcoxon rank-sum tests were used to compare MR imaging parameters on each cartilage subsection between volunteers and patients for those MR imaging parameters found to be significantly different for the entire knee joint.

Receiver operating characteristic analysis was used to assess diagnostic performance with $T2_{Single}$, $T2_F$, $T2_S$, and F_F values on MR images of each cartilage subsection for differentiation of morphologically normal cartilage from cartilage with morphologic degeneration and for differentiation of morphologically normal cartilage from cartilage with mild morphologic degeneration. To determine the severity of morphologic cartilage degeneration on MR images, a normalized BLOKS score was calculated by dividing the BLOKS score of each cartilage subsection by the maximum possible BLOKS score in the subsection. Morphologically normal cartilage was defined as a cartilage subsection with a BLOKS score of 0 (104 subsections in volunteers and 24 subsections in patients), cartilage with morphologic degeneration was defined as a cartilage subsection with a BLOKS score greater than 0 (88 subsections in patients), and cartilage with mild morphologic degeneration was defined as a cartilage subsection with a normalized BLOKS score greater than 0 but less than 0.3 (64 subsections in patients). Areas under the curve (AUC) were calculated to assess diagnostic performance. Differences in AUCs among $T2_{Single}$, $T2_F$, $T2_S$, and F_F were compared by using a previously described methodology (41).

Results

The coefficients of variation for multicomponent T2 measurements obtained by using the two repeat mcDESPOT sequences on each cartilage subsection of the knee joint ranged from 2.6% for $T2_F$ measurements in the posterior medial femoral condyle to 10.9% for $T2_F$ measurements in the lateral tibial plateau. The coefficients of variation for repeat multicomponent T2 measurements of the entire knee joint were 3.1% for $T2_{Single}$, 1.8% for $T2_F$, 2.2% for $T2_S$, and 1.7% for F_F (Table 1).

Figure 2 shows pixel-by-pixel measurements of $T2_{Single}$, $T2_F$, $T2_S$, and F_F plotted as a function of distance from the bone-cartilage interface to the articular surface. $T2_{Single}$, $T2_F$, and $T2_S$ increased from values of 19.2, 13.9, and 40.8 msec, respectively, at the bone-cartilage interface to values of 56.9, 17.7, and 101.7 msec, respectively, at the articular surface. F_F decreased from a value of 43.0% at the bone-cartilage interface to a value of 16.9% at the articular surface. The percentage of change throughout the depth of the articular cartilage for $T2_{Single}$, $T2_F$, $T2_S$, and F_F was 66.3%, 21.5%, 59.9%, and 60.7%, respectively.

There were higher cartilage $T2_{Single}$ ($P < .001$) and lower cartilage F_F ($P < .001$) values in the entire knee joint in patients with osteoarthritis than in asymptomatic volunteers. There were no significant differences in cartilage $T2_F$ ($P = .079$), $T2_S$ ($P = .124$), and thickness ($P = .143$) values of the entire knee joint between the groups of subjects. The difference in cartilage $T2_{Single}$ and cartilage F_F values between volunteers and patients with osteoarthritis remained significant ($P < .05$) when multivariate analysis was used to account for age differences between the groups of subjects. There were higher cartilage $T2_{Single}$ values in the central medial femoral condyle

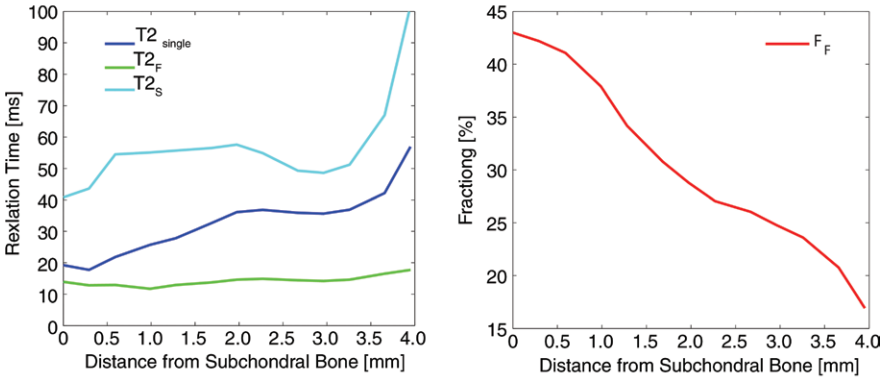
Table 1

Coefficients of Variation for Repeat Multicomponent T2 Measurements

Cartilage Subsection	$T2_{Single}$	$T2_F$	$T2_S$	F_F
Patella	6.4	6.0	5.9	2.8
Trochlea	6.7	5.6	3.7	4.3
Central medial femoral condyle	4.5	5.5	5.7	4.4
Posterior medial femoral condyle	4.0	2.6	2.7	3.9
Central lateral femoral condyle	4.1	3.5	4.0	4.8
Posterior lateral femoral condyle	5.2	4.1	4.7	3.9
Medial tibial plateau	7.4	7.9	5.5	4.4
Lateral tibial plateau	10.0	10.9	9.4	7.3
All	3.1	1.8	2.2	1.7

Note.—Data are percentages.

Figure 2



a. b.

Figure 2: Line graphs show pixel-by-pixel measurements of **(a)** $T2_{Single}$, $T2_F$, and $T2_S$ and **(b)** F_F plotted along linear region of interest extending from cartilage-bone interface to articular surface on single sagittal section through patellar cartilage in randomly chosen 27-year-old asymptomatic male volunteer. Note depth-dependent variations in single component and multicomponent T2 parameters.

(P = .007), posterior medial femoral condyle (P = .015), central lateral femoral condyle (P = .040), posterior lateral femoral condyle (P = .007), and medial tibial plateau (P = .009) in patients than in volunteers. There were lower cartilage F_F values in the trochlea (P = .032), central medial femoral condyle (P = .014), posterior medial femoral condyle (P = .040), central lateral femoral condyle (P = .004), posterior lateral femoral condyle (P = .001), medial tibial plateau (P = .041), and lateral tibial plateau (P = .040) in patients than in volunteers (Table 2). There was a significant difference among volunteers, patients with Kellgren-Lawrence grade 2 knee osteoarthritis, and patients with Kellgren-Lawrence grade 3 knee osteoarthritis for $T2_{Single}$ ($P < .001$), F_F ($P < .001$), and thickness (P = .014) values, but no significant difference for $T2_F$ (P = .173) and $T2_S$ (P = .074) values (Table 3). When multivariate analysis was used to account for age differences among groups of subjects, the difference among volunteers, patients with Kellgren-Lawrence grade 2 osteoarthritis, and patients with Kellgren-Lawrence grade 3 osteoarthritis remained significant for F_F ($P < .05$) values but was no longer significant for $T2_{Single}$ (P = .061) and thickness (P = .355) values. Figures 3 and 4 show $T2_{Single}$, $T2_F$, $T2_S$, and F_F maps of patellar cartilage in an asymptomatic volunteer and a patient with osteoarthritis.

AUC values for F_F, $T2_{Single}$, $T2_F$, and $T2_S$ were 0.753 (95% confidence interval [CI]: 0.690, 0.809), 0.684 (95% CI: 0.618, 0.745), 0.584 (95% CI: 0.515, 0.651), and 0.564 (95% CI: 0.495, 0.631), respectively, for distinguishing between morphologically normal cartilage and cartilage with morphologic degeneration and 0.750 (95% CI: 0.689, 0.801), 0.690 (95% CI: 0.631, 0.748), 0.583 (95% CI: 0.512, 0.652), and 0.571 (95% CI: 0.500, 0.640), respectively, for distinguishing between morphologically normal cartilage and cartilage with mild morphologic degeneration (Fig 5). The use of F_F values showed higher ($P < .05$) AUC values than did the use of $T2_{Single}$, $T2_F$, and $T2_S$ values for distinguishing between normal cartilage and cartilage with degeneration and between normal cartilage and cartilage with mild degeneration. $T2_{Single}$ values showed higher ($P < .05$) AUCs than did $T2_F$ and $T2_S$ values for distinguishing between normal cartilage and cartilage with degeneration and between normal cartilage and cartilage with mild degeneration. However, there was no significant difference in AUC values between $T2_F$ and $T2_S$ for distinguishing between normal cartilage and cartilage with degeneration (P = .227) and between normal cartilage and cartilage with mild degeneration (P = .489).

Discussion

The results of our study demonstrated differences in both single-component and multicomponent T2 parameters of the articular cartilage of the knee joint between volunteers and patients with osteoarthritis of the knee. Cartilage $T2_{Single}$ was significantly higher in patients with osteoarthritis of the knee than in volunteers in our study, which is similar to the findings of previous studies in which the Carr-Purcell-Meiboom-Gill techniques were used to measure $T2_{Single}$ (8–12). Increased $T2_{Single}$ of degenerative cartilage is thought to be due to multiple factors including increased hydration (13), decreased macromolecular content (14–16), and changes in tissue anisotropy due to disruption of the highly organized collagen fiber network (17–19). Cartilage F_F was also significantly lower in patients than volunteers in our study. Previous multicomponent T2-mapping studies (24–26) in which authors used nuclear MR spectroscopy have shown that F_F is strongly correlated with the proteoglycan content of cartilage. Thus, the decreased F_F in patients in our study may be the result of proteoglycan loss in degenerative cartilage that occurs during the early stages of osteoarthritis and gradually worsens as the disease progresses (3,4,42).

Although mcDESPOT and the Carr-Purcell-Meiboom-Gill techniques used in previous nuclear MR spectroscopic studies involve the use of different pulse sequences and reconstruction algorithms to measure multicomponent T2 parameters, there is evidence to suggest that F_F measured by using mcDESPOT also may reflect the proteoglycan content of cartilage. The $T2_F$ values of cartilage measured by using mcDESPOT in our study are similar to values measured by using Carr-Purcell-Meiboom-Gill techniques in previous nuclear MR imaging studies (24–26). In addition, the depth-dependent decrease

Table 2

Average Cartilage Multicomponent T2 Parameters and Cartilage Thickness

Cartilage Subsection	$T2_{Single}$ (msec)		$T2_F$ (msec)		$T2_S$ (msec)		F_F (%)		Thickness (mm)	
	VOL	OA	VOL	OA	VOL	OA	VOL	OA	VOL	OA
Patella	30.2 ± 2.3	33.1 ± 3.8	14.1 ± 0.8	14.8 ± 1.0	52.5 ± 4.2	56.0 ± 5.0	29.9 ± 2.4	28.8 ± 2.7	3.4 ± 0.7	3.1 ± 0.5
Trochlea	38.1 ± 2.9	39.2 ± 2.9	18.4 ± 1.8	17.1 ± 1.3	71.9 ± 5.6	67.9 ± 5.5	29.2 ± 1.5*	27.0 ± 2.1*	2.8 ± 0.4	2.5 ± 0.4
Central medial femoral condyle	32.1 ± 2.9*	37.8 ± 4.2*	16.5 ± 1.5	17.6 ± 1.3	64.2 ± 6.9	68.9 ± 5.8	33.6 ± 1.3*	30.2 ± 3.2*	2.3 ± 0.3	1.9 ± 0.4
Posterior medial femoral condyle	39.6 ± 3.1*	44.4 ± 3.7*	16.5 ± 1.2	17.7 ± 1.3	69.6 ± 5.1	75.1 ± 6.5	29.9 ± 1.8*	27.8 ± 1.7*	2.4 ± 0.3	2.2 ± 0.4
Central lateral femoral condyle	31.0 ± 1.5*	35.3 ± 4.7*	16.6 ± 1.0	16.3 ± 1.9	63.9 ± 5.1	63.7 ± 8.8	33.4 ± 1.7*	30.4 ± 1.7*	2.3 ± 0.2	2.2 ± 0.3
Posterior lateral femoral condyle	36.0 ± 2.1*	40.4 ± 3.3*	16.3 ± 1.3	17.1 ± 1.7	66.9 ± 5.3	69.0 ± 6.3	31.9 ± 1.6*	28.2 ± 1.7*	2.5 ± 0.4	2.3 ± 0.5
Medial tibial plateau	29.8 ± 4.5*	36.0 ± 3.1*	14.1 ± 1.8	16.0 ± 1.2	54.0 ± 8.3	62.4 ± 5.5	31.3 ± 2.7*	28.1 ± 2.7*	1.6 ± 0.4	1.5 ± 0.3
Lateral tibial plateau	31.4 ± 3.6	35.6 ± 4.9	15.0 ± 1.3	15.7 ± 2.1	55.9 ± 6.3	60.5 ± 8.8	30.0 ± 2.1*	27.7 ± 2.4*	2.5 ± 0.5	2.3 ± 0.6
All	33.5 ± 1.6*	37.7 ± 2.3*	16.0 ± 0.5	16.5 ± 0.9	62.4 ± 2.6	65.4 ± 4.0	31.1 ± 1.3*	28.6 ± 1.6*	2.5 ± 0.3	2.3 ± 0.2

Note.—Data are averages ± standard deviation. OA = osteoarthritis, VOL = asymptomatic volunteers.

* Indicates significant difference in values between the groups of subjects, $P < .05$.

in F_F from the bone-cartilage interface to the articular surface in our study correlates well with the depth-dependent decrease in the proteoglycan content of cartilage (43–46). Furthermore, proteoglycan loss due to trypsin degradation of ex vivo bovine cartilage specimens has been shown to decrease F_F significantly in superficial cartilage measured by using mcDESPOT (47). However, additional studies are needed to allow direct correlation of F_F measured by using mcDESPOT with the proteoglycan content of cartilage to determine whether the MR parameter can serve as a sensitive and specific biomarker of proteoglycan in cartilage.

Our study results suggest that F_F may be more sensitive than $T2_{Single}$ for detection of cartilage degeneration in patients with osteoarthritis of the knee and may allow greater diagnostic performance for distinguishing morphologically normal cartilage from morphologically degenerative cartilage at receiver operating characteristic analysis. The improved diagnostic performance of F_F for detection of cartilage degeneration may be due to the fact that F_F is primarily influenced by the proteoglycan content of cartilage, while $T2_{Single}$ is a nonspecific parameter influenced by multiple potentially competing biologic changes that occur during cartilage degeneration. For example, changes in degenerative cartilage such as a reduction in macromolecular content (14–16) and loss of tissue anisotropy due to disruption of the highly organized collagen fiber network (17–19) would result in an increase in $T2_{Single}$. However, this increase in $T2_{Single}$ may be offset partially by simultaneous changes that decrease $T2_{Single}$ such as collagen denaturation, which creates additional sites of interaction between water and collagen molecules (48). Although results of previous studies have shown that $T2_{Single}$ can allow detection of cartilage degeneration in both ex vivo specimens (7) and human subjects (8–12), our results suggest that F_F allows greater diagnostic performance for distinguishing normal from degenerative cartilage. F_F measured by using

mcDESPOT has the additional advantage of being relatively uninfluenced by the magic angle effect, which leads to spurious increases in $T2_{Single}$ when cartilage is oriented at 55° relative to the main magnetic field (49).

Table 3

Average Cartilage Multicomponent T2 Parameters and Cartilage Thickness by Subject Group

Subject Group	$T2_{Single}$ (msec)	$T2_F$ (msec)	$T2_S$ (msec)	F_F (%)	Thickness (mm)
Volunteer	33.5 ± 1.6*	16.0 ± 0.5	62.4 ± 2.6	31.1 ± 1.3*	2.5 ± 0.3*
Kellgren-Lawrence grade					
2	37.8 ± 1.3*	16.4 ± 0.6	65.6 ± 2.2	29.0 ± 1.3*	2.4 ± 0.2*
3	37.6 ± 3.3*	16.7 ± 1.2	65.2 ± 5.9	28.0 ± 1.9*	2.1 ± 0.2*

Note.—Data are averages ± standard deviation.

* Indicates significant difference in values among the groups of subjects, $P < .05$.

In our study, we found that cartilage $T2_F$ and $T2_S$ values were higher in patients with osteoarthritis of the knee than in volunteers, but the differences between the groups of subjects were not statistically significant. Authors of previous nuclear MR spectroscopic studies (24–26) have reported significant increases in $T2_F$ and $T2_S$ after trypsin degeneration of ex vivo cartilage specimens. The increase in $T2_F$ and $T2_S$ may be due to that fact that water tightly and loosely bound to degraded proteoglycan in degenerative cartilage would likely have higher T2 than water bound to the intact macromolecule. The absence of significant

Figure 3

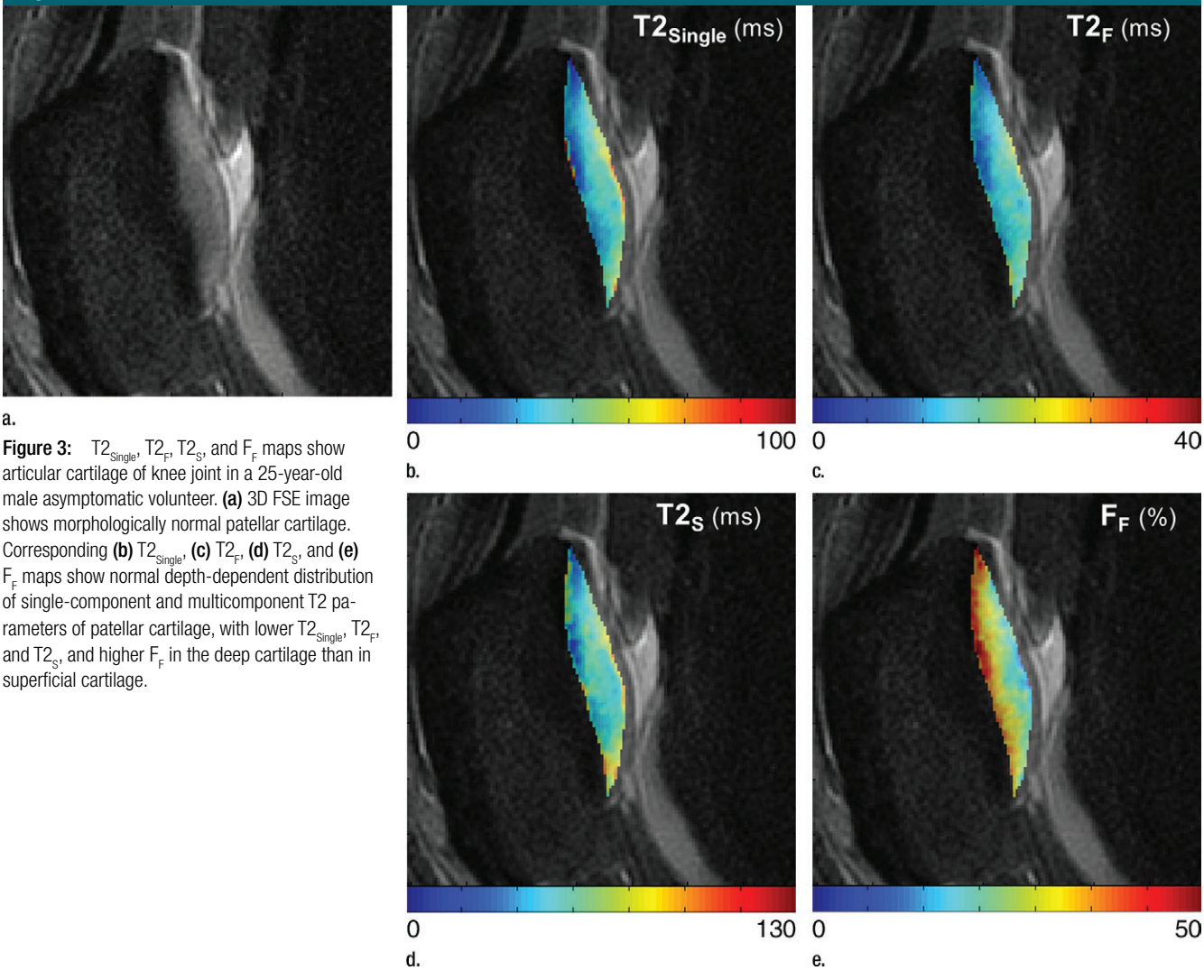


Figure 3: $T2_{Single}$, $T2_F$, $T2_S$, and F_F maps show articular cartilage of knee joint in a 25-year-old male asymptomatic volunteer. **(a)** 3D FSE image shows morphologically normal patellar cartilage. Corresponding **(b)** $T2_{Single}$, **(c)** $T2_F$, **(d)** $T2_S$, and **(e)** F_F maps show normal depth-dependent distribution of single-component and multicomponent T2 parameters of patellar cartilage, with lower $T2_{Single}$, $T2_F$, and $T2_S$, and higher F_F in the deep cartilage than in superficial cartilage.

Figure 4

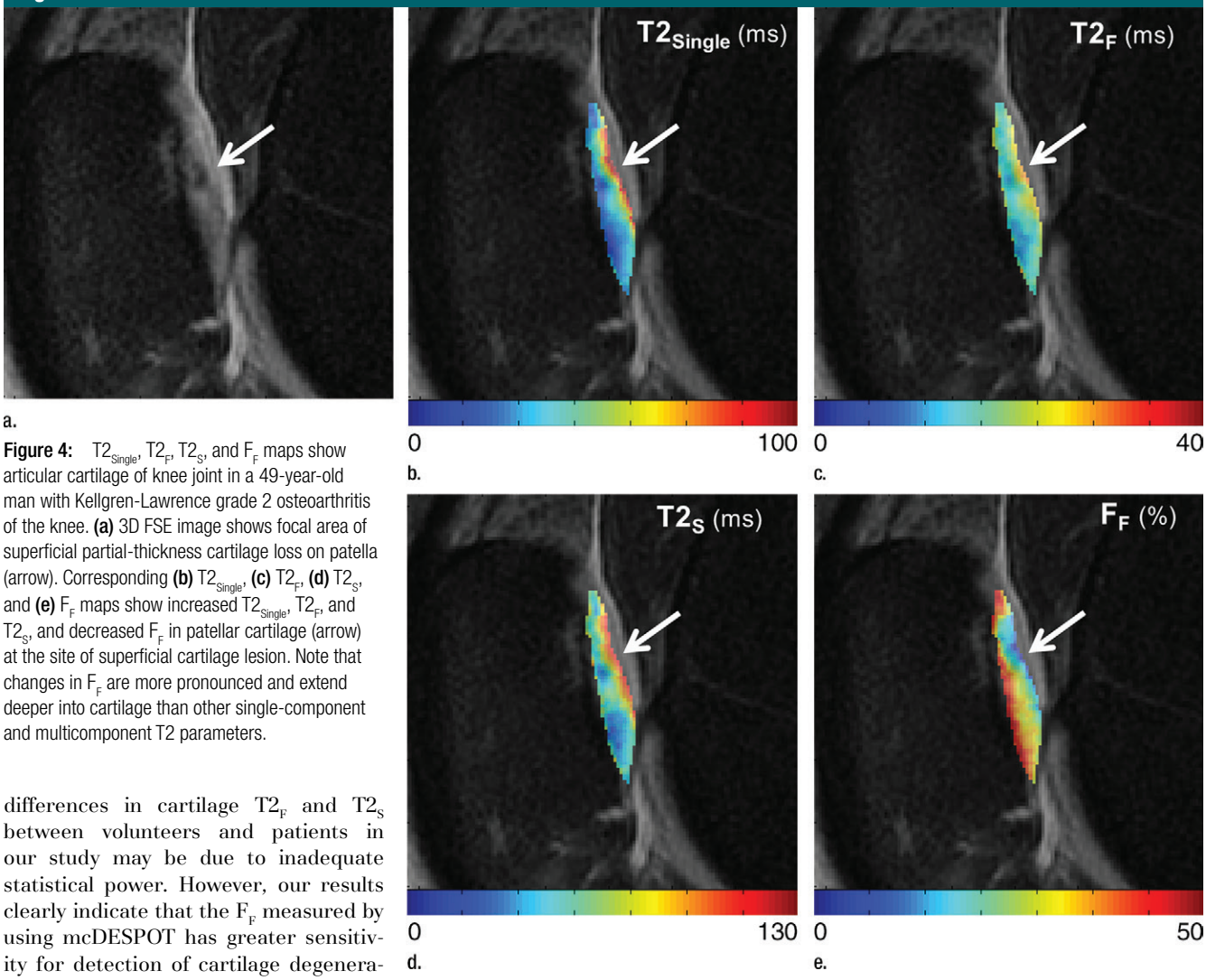


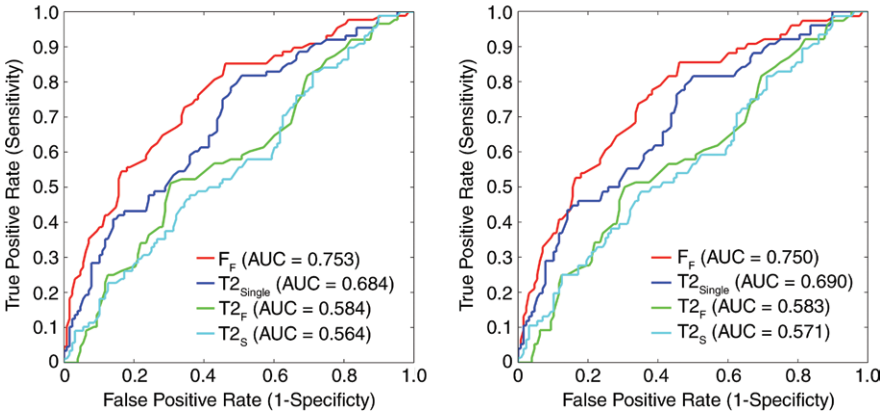
Figure 4: $T2_{Single}$, $T2_F$, $T2_S$, and F_F maps show articular cartilage of knee joint in a 49-year-old man with Kellgren-Lawrence grade 2 osteoarthritis of the knee. **(a)** 3D FSE image shows focal area of superficial partial-thickness cartilage loss on patella (arrow). Corresponding **(b)** $T2_{Single}$, **(c)** $T2_F$, **(d)** $T2_S$, and **(e)** F_F maps show increased $T2_{Single}$, $T2_F$, and $T2_S$, and decreased F_F in patellar cartilage (arrow) at the site of superficial cartilage lesion. Note that changes in F_F are more pronounced and extend deeper into cartilage than other single-component and multicomponent T2 parameters.

differences in cartilage $T2_F$ and $T2_S$ between volunteers and patients in our study may be due to inadequate statistical power. However, our results clearly indicate that the F_F measured by using mcDESPOT has greater sensitivity for detection of cartilage degeneration than does the T2 of each individual water component. The T2 of cartilage is a composite measure of the T2 values and fractions of the individual water components of cartilage, which are independent characteristics of the tissue. The limited diagnostic performance of $T2_F$ and $T2_S$ for distinguishing normal from degenerative cartilage may be responsible for the decreased diagnostic performance with $T2_{Single}$ compared with that with F_F.

Studies to investigate how cartilage degeneration in human subjects leads to changes in the fractions and T2 values of the different water components of cartilage have not been performed previously because of the long imaging times of Carr-Purcell-Meiboom-Gill techniques currently used for multicomponent T2 mapping. Multicomponent T2*-mapping techniques have been used to assess the fast and slow-relaxing water components of human articular cartilage (50,51). In a previous study (50), authors investigated multicomponent T2* parameters of human cadaveric patellar cartilage specimens and showed an increased F_F in degenerative cartilage, which the authors attributed to greater binding between water and degraded collagen fibers. However, multicomponent T2*-mapping techniques use extremely short echo times which can detect signal from the extremely fast-relaxing water tightly bound to the collagen component of cartilage. Furthermore, multicomponent T2* parameters of cartilage are influenced by magnetic field inhomogeneity and inherent differences in tissue susceptibility that may change with varying degrees of degeneration and may not reflect the true T2 characteristics of the different water components of cartilage. Thus, multicomponent T2- and T2*-mapping techniques likely provide uniquely different but perhaps complementary information regarding the composition and ultrastructure of articular cartilage.

Our study had several limitations. One limitation was the relatively small

Figure 5



a. b.

Figure 5: Receiver operating characteristic curves with AUCs showing diagnostic performance with average $T2_{Single}$, $T2_F$, $T2_S$, and F_F values in each cartilage subsection to differentiate between **(a)** morphologically normal cartilage and cartilage with morphologic degeneration and between **(b)** morphologically normal cartilage and cartilage with mild morphologic degeneration. F_F showed significantly higher ($P < .05$) AUC values than did other single-component and multicomponent T2 parameters, indicating greater diagnostic performance.

number of subjects, which may have been responsible for the failure to find statistically significant differences in cartilage $T2_F$ and $T2_S$ between volunteers and patients. In addition, all patients in our study were much older than the volunteers and had well-established Kellgren-Lawrence 2 or advanced Kellgren-Lawrence 3 grades of the disease. The presence of definitive osteophytes is the radiographic hallmark of osteoarthritis (36,37). We felt that it was important that the initial validation of mcDESPOT for detection of differences between volunteers and patients should include volunteers without senescence-related changes in cartilage composition and ultrastructure and patients whose osteoarthritis was diagnosed by using standard clinical and radiographic criteria. Another limitation of our study was the use of the relatively insensitive reference standard of morphologic MR imaging results for determining the presence or absence of cartilage degeneration in the knee joint. Additional studies with surgical or histologic correlation are needed to determine whether multicomponent T2 parameters measured by using mcDESPOT can allow detection of cartilage degeneration during the earliest stages of the disease process. Furthermore, the repeatability of cartilage multicomponent T2 measurements obtained by using mcDESPOT was assessed only in volunteers and not in patients. Another limitation of our study was that global regions of interest within cartilage were used to compare multicomponent T2 parameters between volunteers and patients. Because of the depth-dependent variations of multicomponent T2 parameters, comparison of MR parameters in the superficial and deep layers of cartilage may have provided higher discriminatory power between groups of subjects. However, dividing the cartilage into superficial and deep layers would have been extremely difficult and the results would have been prone to partial volume artifacts, given the 0.6-mm in-plane spatial resolution of the multicomponent T2 maps, especially in the evaluation of the thin articular cartilage in patients. A final limitation was relatively long imaging time of the mcDESPOT sequence, which may limit its use in the clinical setting. However, we are currently investigating various methods to reduce the imaging time of the mcDESPOT sequence, including use of a smaller number of optimized spoiled gradient-echo and balanced steady-state free-precession sequences, more rapid methods for estimating the B_0 and B_1 fields, and use of parallel imaging.

In conclusion, our study results have shown that patients with osteoarthritis of the knee have significantly higher cartilage $T2_{Single}$ and significantly lower cartilage F_F values than do asymptomatic volunteers. Our results suggest that F_F measured by using mcDESPOT may be more sensitive than $T2_{Single}$ for detection of cartilage degeneration in patients with osteoarthritis of the knee and may allow greater diagnostic performance for distinguishing between morphologically normal cartilage and morphologically degenerative cartilage at receiver operating characteristic analysis. The mcDESPOT sequence may provide an improved quantitative MR imaging technique for evaluating articular cartilage at 3.0 T. However, further studies are needed to better understand the mechanisms responsible for changes in multicomponent T2 parameters in patients with osteoarthritis and to investigate the ability of mcDESPOT to allow detection of cartilage degeneration in clinical practice and to monitor changes in cartilage composition and ultrastructure in osteoarthritis research studies.

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